

claims were rejected under 35 U.S.C. 101 on the basis that the disclosed invention allegedly is inoperative and lacks utility. Additionally, all claims were rejected under 35 U.S.C. 102(b) or (e) as anticipated by cited references. Also, all of the claims were rejected under 35 U.S.C. 103 as obvious over a series of references. Further, all of the claims stand rejected under 35 U.S.C. 112, first paragraph as not having enabling support in the disclosure. Further still, all of the claims were rejected under 35 U.S.C. 112 for containing "new matter." Finally, the specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide both an enabling disclosure and support for the claimed invention. In view of the following remarks and accompanying declaration by co-inventor Dr. Kevin W. Moore, the Examiner is respectfully requested to withdraw these rejections and allow Claims 20-25, all of which are considered to be in proper form for allowance.

Since the subject invention was reviewed on pages 3 and 4 of applicants' response dated September 20, 1985, no additional general discussion will be presented, but specific elements will be discussed in connection with each individual rejection by the Examiner. The interview with the Examiner on November 21, 1985, is gratefully acknowledged. The substance of that interview is included and expanded upon in the following remarks.

Claim 1 has been amended to emphasize the fact that the claimed light and heavy polypeptide chains consist of a variable region or a portion of the variable region without constant region amino acids. Support for this amendment may be found in the Specification at page 2, lines 35 to 38 and page 4, lines 14 to 18.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide support for the claimed invention. Also, Claims 20-25 are rejected under 35 U.S.C. 112, first paragraph, for allegedly failing to have support in the specification for the amendment to Claim 20 made in applicants' September 20, 1985 response. These rejections are respectfully traversed.

Two substitutions and deletions were made in Claim 20 by the September 20, 1985 response. First, in order to clarify the process by which DNA sequences direct the synthesis of polypeptides, the word expression was substituted for the word translation. Those skilled in the art would readily appreciate the distinction in the two terms. Translation refers to the process of using the genetic information present in mRNA to produce a polypeptide, whereas expression is a more expansive term and includes transcription in addition to translation. In order to proceed from the DNA sequence coding for the variable region to a polypeptide, both transcription and translation are required. Therefore, one skilled in the art appreciates that the claimed product requires a process known as "expression." Further, support is found in the specification at page 17, lines 1 to 3 and at numerous other locations in the application.

Second, the amendment of September 20, 1985 to Claim 20 included the deletion of "free of the" and added "said expression occurring in the absence of expression of a DNA sequence coding for natively associated (constant region)." These terms refer to the inclusion of a DNA sequence coding for the constant region in the subject vectors. It is an accepted axiom that a disclosure's compliance with the written description requirement of 35

U.S.C. 112, first paragraph, is determined by whether the disclosure of the application as originally filed reasonably conveys to the artisan at the time of filing that the inventor had possession of the later claimed subject matter. It is not necessary that the claimed subject matter be described in haec verba to satisfy the description requirement. The claim limitations only need to be described clearly, so that one having ordinary skill in the pertinent art would recognize from the disclosure that the applicants' invention included those limitations.

Clearly, the insertion of the added phrase finds support in the basic theme of the entire application. A major aspect of the invention is the concept that the claimed rFv binding compositions are comprised of light and heavy chain variable regions that are just that, variable. The entire construction scheme for the expression vectors revolves around producing DNA sequences lacking in the constant region. Surely, for one skilled in the art, the use of this phrase is intuitively obvious as a valid and disclosed substitute for "free of the" constant region. For these reasons the Examiner is respectfully requested to remove his rejection of the claims under 35 U.S.C. 112, first paragraph, concerning "new matter."

Claims 20-25 were examined and rejected under 35 U.S.C. 101 because the invention as disclosed is allegedly inoperative and therefore lacks utility. The Examiner's rejection is elaborated on pages 2 and 3 of the Office Action dated June 6, 1983. It is argued by the Examiner that there is no showing that the cloned genes can be transcribed and translated in any bacterial host nor that the polypeptides would be "assembled" post-translationally into a functioning antibody, nor that the properly assembled

antibody would be recoverable in active form. These rejections are respectfully traversed.

The burden of proof is initially placed upon the Patent Office to explain why a patent application disclosure may be considered inoperative or non-enabling. This explanation must be supported by clear evidence, such as contrary teachings in the art. With this consideration in mind, the Examiner is respectfully requested either to support with evidence the position that the disclosure is inoperative or to withdraw the rejection.

Further, as the Examiner is aware, no working examples need be given for the subject application if one skilled in the art would be capable of practicing the subject invention without "undue experimentation." "Undue experimentation" does not include periods of time required to conduct routine refinements of the disclosed procedure, even though a considerable amount of time is expended. The subject application fully describes the expression, purification, and assembly of the variable region chains into active rFv species throughout the subject specification; see, page 16, line 24 through page 18, line 24 and page 41, line 12 through page 42, line 14.

Co-inventor Dr. Kevin W. Moore is an individual skilled in the relevant art. Dr. Moore has thoroughly reread the subject application and analyzed the disclosure in conjunction with the cited art. In his attached Declaration, submitted under 37 C.F.R. 1.132, he states that all of the enabling features of the subject invention (expression, isolation, and assembly of an active species) that are disputed by the Examiner are indeed discussed in more than sufficient detail to allow one skilled in the art (e.g., a molecular biologist or the equivalent) to practice

the subject invention. Dr. Moore has carefully reviewed the relevant art and as he points out in his Declaration, both the Boss et al. and Wood et al. references illustrate the practicality of the subject application's recombinant DNA techniques in the production of functional specific binding compositions. Couple this with the showing in Ehrlich et al. and Sharon et al. that enzymatically generated variable region containing polypeptide fragments renature to form active binding species, as also discussed by Dr. Moore in his Declaration, there can be little doubt of the operability of the present invention, and the rejection under 35 U.S.C. 101 should be withdrawn.

Claims 20-25 were examined and rejected under 35 U.S.C. 102(b) as anticipated by Sharon et al., Roseblatt et al., or Pawlowski et al. The Examiner argues that there has been no patentable distinction pointed out between the claims and these cited references. These rejections are respectfully traversed.

For a 102(b) rejection to be valid, the cited reference must "identically describe" the claimed subject invention "within the four corners" of that reference. Claim 20 is clearly limited to rFv compositions prepared by recombinant DNA expression wherein the DNA coding sequences lack the sequence region coding for the constant regions of the heavy or light polypeptide chains. Sharon et al. fails to anticipate the subject invention rFv species since in Sharon et al. the fragments were produced by first enzymatically cleaving the light chain with trypsin, combining the resultant digest with heavy chain, and finally using papain digestion to produce their product. This procedure does not make use of the recombinant DNA techniques to produce their

binding species and more importantly, these fragments are not free of the constant region amino acids.

As for the Roseblatt et al. reference, no recombinant DNA procedures were employed and the immunoglobulin fragment that was determined to be active for specific binding contained an intact light chain. Clearly, this article also does not anticipate the claimed subject invention.

The Pawlowski et al. reference deals with antibodies used to identify and purify collagen-synthesizing polysomes. Such antibodies are quite distinct from the recombinant rFv compositions claimed in the subject application. Among numerous distinctions between the two types of antibody-based compositions is the difference that the constant regions are still present in the reference's antibodies, whereas they are specifically missing in the claimed rFv compositions. Further, the claimed rFv compositions were produced by recombinant DNA technology, while the article refers to traditional antibodies.

For the above reasons, the use of these three articles is not justified to form the basis for a 35 U.S.C. 102(b) rejection. The Examiner is thus respectfully requested to withdraw this rejection of Claims 20-25.

Claims 20-25 were rejected under 35 U.S.C. 103 as being unpatentable over Zakut et al., Seidman et al. or Early et al., in view of Amster et al. and further in view of the applicants' statement on page 40, first full paragraph, of the subject application or Ptashne et al. The Examiner argues that the state of the art cited in these references makes obvious the subject invention. Further, the Examiner argues that it is not apparent from the record that constant region polypeptides are necessarily produced

by the cited art. These rejections are respectfully traversed.

First, as was stated in applicants' response of September 20, 1985, applicants do not dispute that the sequences disclosed in the subject application are derived from Seidman et al. and Early et al., nor that Amster et al. alludes to bacterial hosts for synthesizing antibodies. Further, Zakut et al., Ptashne et al. and page 40 of the subject application merely state the level of art at the time of the invention. None of these references alone or in combination make obvious the claimed subject invention.

Zakut et al. clearly states that the transformants were screened by hybridization with a cDNA fragment derived from the 5' portion of the constant region of a heavy chain. Since this is the case, the detected transformants must, of necessity, contain at least a portion of the constant region. Therefore, this reference teaches away from the subject invention which claims constant region free rFv compositions.

Seidman et al. teaches the sequence found in the variable region of a light chain, but does not teach how or if such a fragment could be produced or expressed nor how it could serve as a useful component of a specific binding species. Likewise, Early et al. discloses sequences for variable regions of heavy chains, but does not in any way teach constructs comprising only the variable region with or without association to a light chain.

Amster et al. is directed to fused expression products that contain a light chain region or a portion of a light chain region in which part of the variable region and all of the constant region are present. The claimed rFv compositions of the subject invention are completely

different since no fused region is present, and it is the constant region that is missing, not a portion of the variable region with an intact constant region. The reference suggests the possibility of the synthesis of specific antibody molecules in bacteria not rFv compositions lacking a constant region.

Ptashne et al. merely relates a general procedure for protein production in bacteria. This procedure is only one of many tools required to create the subject invention and in no way makes obvious the claimed rFv compositions. No suggestion is made of employing anything other than DNA coding for native proteins.

Taken either individually or as a whole, these cited references do not teach the subject invention nor do they make the claimed rFv composition obvious. In fact, they teach away from the claimed rFv composition since only constructs are proposed that contain the constant region of the heavy or light chains. As the Examiner is fully aware, "obvious to try" is not the standard by which obviousness is to be measured. The Examiner's rejection under 35 U.S.C. 103 is respectfully requested to be withdrawn.

Claims 20-25 have been examined and rejected by the Examiner under 35 U.S.C. 102(b) or (e) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Ehrlich et al. Since Auditore is still mentioned in paragraph 26 of the Office Action, it is presumed that the 102(b) rejection under Auditore, as to its prior art, still applies.

First, neither Ehrlich et al. nor Auditore "identically describe" the claimed subject rFv compositions "within the four corners" of the reference. Clearly, the various antibodies and antibody hybrids described in Columns

1 and 2 of Auditore do not anticipate the subject rFv compositions since enzymatic means were employed to generate the variable region fragments. Such enzyme generated fragments would contain some of the constant region unlike the claimed rFv compositions. Ehrlich et al. produced what they termed the variable region of a light chain by mild acid hydrolysis followed by affinity chromatography directed to bind selectively the constant region of the chain. However, even mild acid hydrolysis is not totally selective and the non-bound eluate off the affinity column would contain quantities of variable length polypeptides including ones with a portion of the constant region (see, column 12 of Ehrlich et al.). As for their heavy chain variable region preparation, since cathepsin B was used to enzymatically cleave the chain, portions of the constant region would still be linked to the variable region. It should be apparent from this analysis that the 35 U.S.C. 102(b) rejections should be withdrawn and this is respectfully requested.

As for the 35 U.S.C. 103 obviousness rejection, the cited references in the Auditore patent merely relate to the above-mentioned antibodies and antibody hybrids prepared by traditional means and does not suggest the subject rFv invention since at least a portion of the constant region was present in all of the referenced species. Likewise, the Ehrlich et al. patent deals with polypeptide species that contain to a lesser or greater extent some portions of the constant region amino acids.

Until the subject rFv compositions were described by the applicants, no such species had been disclosed. Auditore and Ehrlich et al. may have stimulated interest in the general area of antibody fragmentation and invited

researchers to experiment, but as pointed out above, "obvious to try" is not the standard to measure obviousness. Further, no means to produce the claimed compositions were proposed. Applicants have provided a detailed procedure for producing a novel rFv composition not even contemplated by others. The Examiner is respectfully requested to withdraw this last rejection.

Claim 20 has been amended in accordance with the Examiner's suggestions. By limiting Claims 20-25 to "mammalian" immunoglobulin the rejections to these claims and the specification under 35 U.S.C. 112, first paragraph have been avoided.

It is therefore respectfully submitted that for all of the above reasons, applicants' claims are patentable over the cited references. Thus, in view of the above amendments and the additional remarks, the Examiner is respectfully requested to allow Claims 20-25, as amended, and pass this application to issue.

If for any reason the Examiner feels that a telephone conference would in any way expedite prosecution of the subject application, the Examiner is invited to telephone the undersigned at (415) 493-2590.

Respectfully submitted,

TOWNSEND and TOWNSEND

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Dated 4-10-86

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